

(19)



Europäisches Patentamt

European Patent Office

Office européen des brevets



(11)

EP 0 992 238 A1

(12)

EUROPEAN PATENT APPLICATION

(43) Date of publication:

12.04.2000 Bulletin 2000/15

(21) Application number: **99100030.8**

(22) Date of filing: **04.01.1999**

(51) Int. Cl.⁷: **A61K 31/085**, A61K 31/14,

A61K 31/44

// (A61K31/14, 31:085),

(A61K31/44, 31:085)

(84) Designated Contracting States:

**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE**

Designated Extension States:

AL LT LV MK RO SI

(30) Priority: **06.10.1998 US 167225**

05.11.1998 US 186825

(71) Applicant:

**I-Dent International Corporation
Bellport, New York 11713 (US)**

(72) Inventor: **Libin, Barry**

Bellport, New York 11713 (US)

(74) Representative:

**Becker Kurig Straus
Patentanwälte**

**Bavariastrasse 7
80336 München (DE)**

(54) **Use of triclosan for preventing and treating mucosal and dermal conditions**

(57) A method of treating mucositis, herpetic infections or fungal infections by contacting the affected area with an amount of composition which comprises triclosan or a combination of triclosan and a cationic antibacterial compound in an amount which is effective to alleviate the symptoms of the particular condition.

EP 0 992 238 A1

Description

[0001] Many conditions arise which cause moderate to acute discomfort on the skin and mucous membranes. In particular, immunodeficient states may cause mucositis with accompanying inflammation; herpetic lesions may cause inflammation and fungal infections are also accompanied by inflammation.

[0002] Immunodeficient patients frequently exhibit a condition on the oral mucosa which is clinically described as oral mucositis. This condition has no known microbial or viral vector that has been implicated as the causative agent. The immunodeficiency that preceded the appearance of mucositis may arise spontaneously from genetic factors, may be caused by infections, e.g., the HIV virus or mucositis be induced as a result of chemotherapy or radiation therapy for neoplastic diseases. This condition has been difficult to treat and has not responded to treatment with antimicrobial or other agents.

[0003] The infections caused by Herpes simplex may appear anywhere on the skin or mucosa but are most often seen around the mouth, lips, conjunctiva, cornea and genitalia accompanied by an inflammatory response which causes pain and various degrees of discomfort. There are two existing types of herpes simplex virus infections, each type having multiple strains. Type 1 herpes simplex infects mucous membranes of the oral cavity as well as perioral skin, the skin above the waist and the eyes. A serious herpes simplex Type 1 infection is herpes keratitis which may result in disfunction of the cornea. Other primary herpes simplex Type 1 infections include stomatitis and dermatitis.

[0004] Herpes simplex Type 2 causes genital infections and is the second most common venereal disease not only in the United States but in many other countries.

[0005] It has been found that when the immune system is compromised as in the case of patients undergoing chemotherapy for cancer, the patients become highly susceptible to herpes simplex infections.

[0006] A large percentage of the U.S. population is affected by some form of a herpes virus infection, there being an estimated 98 million cases of herpes labialis (Type 1) occurring each year. In the case of genital herpes (Type 2) there are about 30 million cases each year.

[0007] Herpes simplex (Type 1) resides in latent form in the trigeminal ganglions in the facial area. In some individuals this virus remains inactive while in many others the virus may travel from the nerves located near the cheek bone to the lips. This gives rise to vesiculo-ulcerative eruptions around the lips, the chin and the cheeks, or under the nose.

[0008] Herpes simplex consists of evolving strains that are resistant to known anti-viral agents such as ganciclovir and acyclovir. Because herpes simplex infections are not treatable by known antiviral agents, the usual protocol for such infections includes the elimination of the conditions which precipitated the viral infections and local antibiotic treatment to prevent bacterial infection at the site of the viral infection. But an antibiotic, such as penicillin is a bactericidal agent and as such is ineffective against a herpes simplex infection.

[0009] Unicellular fungi may cause dermal, mucosal or periodontal opportunistic infections. The incidence of such infections has risen with the increase in the number of immunocompromised patients, such as those suffering from HIV infections, transplant recipients treated with immunosuppressive drugs and patients undergoing chemotherapy and radiation therapy for cancer.

[0010] In the article entitled "In Vitro Antifungal Properties of Mouthrinses Containing Antimicrobial Agents" by Giuliana et al., in J. Periodontal 1997; 68:791-801 it is noted that mouthrinses containing an antimicrobial agent, such as Triclosan or CPC might serve as an appropriate alternative to conventional antifungal drugs in the management of oral candidiasis.

[0011] It has been discovered that an alternative to conventional antifungal drugs is a composition in accordance with the invention in which a non-cationic antimicrobial agent combined synergistically with a cationic antimicrobial agent. This composite is also effective as a topical agent, in the form of an ointment or spray against superficial fungal infections.

[0012] This may include fungal infections of the head (tinea capitis), body infections (tinea corporis), "athlete's foot" (tinea pedis) as well as groin and buttocks infections (tinea cruris). The composite has also been found to be effective against superficial candidiasis (moniliasis) and cutaneous candidiasis. Infections caused by candida are grouped under the term candidiasis and these infections involve the mucous membranes, scalp, skin and nails and may be accompanied by pain, itching and/or redness. The treatment of candida infections is discussed in MacNeill et al. J.Clin. Periodont. 24; 733-760 (1997), which is incorporated by reference.

[0013] The applicant has discovered a treatment for the inflammation which accompanies mucositis, herpetic infections and fungal infections which is based on contacting the diseased sites on the affected area of the mucosa with triclosan alone or in combination with a cationic antimicrobial compound. The present inventor holds U.S. 5,236,699, which is incorporated by reference. That patent describes the use of a mouth rinse which contains triclosan and a cationic antimicrobial agent for use inter alia the treatment of plaque and gum diseases.

[0014] The present invention comprises a new composition for the prevention or treatment of mucositis, herpetic infections and fungal infections which comprises applying to the affected area an effective amount of a composition which comprises triclosan alone or in combination with a cationic antimicrobial compound.

[0015] It is a primary object of the invention to provide a composition for treating the prevention or treatment of mucositis, herpetic infections and fungal infections.

[0016] It is also an object of the invention to provide a composition for treating the inflammation of oral mucositis in immunocompromised patients.

[0017] It is also an object of the invention to provide a composition for treating inflammation caused by herpetic infections.

[0018] It is also an object of the invention to provide a composition for treating inflammation caused by fungal infections.

[0019] It is also an object of the invention to provide a composition for treating mucositis, herpetic infections or fungal infections using triclosan alone or in combination with a cationic antibacterial compound.

[0020] These and other objects of the invention will become apparent from a review of the appended specification.

[0021] The above-identified objects were solved by the composition according to claim 1.

[0022] The subclaims contain special embodiments of the present invention.

[0023] Mucositis, herpetic infections or fungal infections such as candidiasis are treated in accordance with the present invention by contacting the involved area with a composition which contains an amount of triclosan which is effective to treat the particular condition. Generally these compositions contain about 0.01 to 5.3wt% and preferably 0.02 to 0.5wt% of triclosan. Generally, semi-solid formulations will be formulated with higher levels of triclosan. The amount of the formulation which is applied will depend on the extent of the lesion. Generally when a liquid formulation is applied to a typical lesion, from 5ml to 30ml is applied to the lesion as a mouth rinse with the patient being instructed to eject the excess amount of the formulation from the mouth without swallowing. If a semi-solid formulation is used, then a thin film, i.e. from 0.5mm to 5mm in thickness may be applied to the affected area.

[0024] Triclosan is 2,4,4'-trichloro-2'-hydroxydiphenyl ether which is commercially available.

[0025] The triclosan is adsorbed and retained on the oral mucosa while resisting removal by saliva in the oral cavity.

[0026] The compositions may be prepared as a liquid or a semi-solid formulation. The semi-solid compositions may vary from highly viscous liquids to gels or paste like formulations.

[0027] A liquid formulation may be prepared with purified water, triclosan and a solubilizer. The solubilizer may comprise a sodium lauryl sulfate, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, poloxamer or mixtures thereof. The poloxamers are of the formula $\text{HO}(\text{CH}_2\text{CH}_2\text{O})_a(\text{CH}-(\text{CH}_3)(\text{CH}_2\text{OH})_b(\text{CH}_2\text{CH}_2\text{O})_c\text{H}$ where b is at least 15 and $(\text{CH}_2\text{CH}_2\text{O})_a + c$ is varied from 20 to 90% by weight and the weight average mol wt ranges from 10,000 to >16,000. The polyoxamers are available under the Pluronic trademark and Pluronic F127 is a preferred solubilizer. If a solubilizer is employed, it will comprise from 0.5 to 8wt% of the liquid composition. Generally, only liquid compositions in water will require a solubilizer; semi-solid formulations will not require the presence of a solubilizer.

[0028] The mucositis treating formulation may include an anti-caries agent which is soluble in water such as sodium fluoride, stannous fluoride or sodium monofluorophosphate in an amount which is effective to inhibit tooth decay in an immunocompromised patient. Generally, this amount will be from 0.01 to 4% by weight, based on the weight of the fluoride ion. The amount may be varied depending on the particular source of the fluoride ion which is chosen. Certified color may be added in a minor amount e.g. 0.1% by weight. FD&C Blue No.1 or FD&C Yellow No.5 may be used as desired.

[0029] If a cationic antibacterial agent is used in combination with the triclosan, it may be used in combination with chlorhexidine and quaternary ammonium salts such as cetylpyridinium chloride (CPC) which is the monohydrate of the quaternary ammonium salt of pyradine and cetyl chloride. CPC is cationic, highly soluble in water and alcohol. Other cationic antimicrobial agents include benzalkonium chloride, benzethonium chloride, methylbenzethonium chloride and domiphen bromide. Chlorhexidine may be applied as the free base, or as the dihydrochloride or the gluconate salt. The composition may alternatively be based on an anionic antimicrobial agent (e.g., potassium sorbate; sodium benzoate; or methyl or propyl paraben).

[0030] The combination of triclosan and the cationic antimicrobial compound has the effect that the combined agents are readily adsorbed and retained on the oral mucosa while resisting removal by saliva in the oral cavity.

[0031] The compositions may be prepared as a liquid or a semi-solid formulation. The semi-solid compositions may vary from highly viscous liquids to gels or paste like formulations.

[0032] A liquid formulation may be prepared with purified water, the triclosan, the cationic antimicrobial compound and a solubilizer. The solubilizers have been described supra.

[0033] A typical liquid formulation will comprise:

	%weight
triclosan	0.100

EP 0 992 238 A1

(continued)

	%weight
CPC	0.024
Sorbitol Solution, U.S.P.	12.000
Glycerin	10.000
Sodium Saccharin, U.S.P	0.100
Pluronic FI27, NF	4.000
190 Proof Grain Alcohol, U.S.P.	7.000
Peppermint IFL2745	0.152
Caramel Color AP100	0.0085
Purified water	66.615

[0034] A typical fluoridated liquid formulation will comprise:

	%weight
triclosan	0.100
CPC	0.024
Sodium Fluoride	0.020
Sorbitol Solution, U.S.P.	11.980
Glycerin	10.000
Sodium Saccharin, U.S.P	0.100
Pluronic FI27, NF	4.000
190 Proof Grain Alcohol, U.S.P.	7.000
Peppermint IFL2745	0.152
Caramel Color AP100	0.0085
Purified water	66.615

[0035] A typical semisolid formulation which is a cream: will include:

5	triclosan	0.1-5.3wt%
	Cetaryl glucoside and cetaryl alcohol (Emulgade PL 68/50, Henkel)	0.5-6.7wt%
	Cetaryl alcohol (Lanette, Henkel)	0.5-7.7wt%
	Coco-Caprylate (Cedol LC, Henkel)	0.5-6.0wt%
10	Dicapryl ether (Cetiet, Henkel)	0.25-5.0wt%
	Sweet almond oil	0.25-5.0wt%
	Petrolatum	0.5-6.0wt%
	Dimethicone (Silicone DC 200CS/Dow)	0.1-5wt%
15	Phase B	
	CPC	0.01-4.4wt%
	glycerin	0.5-4.6wt%
20	Sodium methylparaben/Sodium paraben	0.01-0.03wt%
	or	
	Sodium benzoate	0.25-0.3wt%
25	Deionized water	10-90wt%

[0036] An example of a semi-solid formulation according to the invention is as follows:

30	Phase A	
	triclosan	0.3wt%
	Cetaryl glucoside and cetaryl alcohol (Emulgade PL 68/50, Henkel)	3.7wt%
35	Cetaryl alcohol (Lanette, Henkel)	3.7wt%
	Coco-Caprylate (Cedol LC, Henkel)	3.0wt%
	Dicapryl ether (Cetiet, Henkel)	2.0wt%
40	Sweet almond oil	2.0wt%
	Petrolatum	3.0wt%
	Dimethicone (Silicone DC 200CS/Dow)	0.6wt%

50	Phase B	
	CPC	0.1wt%
	Glycerin	2.6wt%
55	Sodium methylparaben	0.18wt%
	Sodium paraben	0.02wt%
	Deionized water to	100.0wt%

5

Phase C	
Tocopheryl acetate (cophenol 1260/Henkel)	1.0wt%

10 [0037] The composition is prepared by separately heating Phase A and Phase B to 80°C prior to forming these phases. Phase C is added with stirring at 55°C until a smooth homogeneous mixture is obtained.

[0038] The foregoing description of a preferred embodiment of the invention has been presented for purposes of illustration and description. It is not intended to be exhaustive or to limit the invention to the precise form disclosed. Obvious modifications or variations are possible in light of the above teachings. All such obvious modifications and variations are intended to be within the scope of the appended claims. A typical liquid formulation will comprise:

15

	%weight
triclosan	0.100
Sorbitol Solution, U.S.P.	12.000
Glycerin	10.000
Sodium Saccharin, U.S.P	0.100
Pluronic FI27, NF	4.000
190 Proof Grain Alcohol, U.S.P.	7.000
Peppermint IFL2745	0.152
Caramel Color AP100	0.0085
Purified water	66.639

20

25

30

35 [0039] A typical fluoridated liquid formulation will comprise:

	%weight
triclosan	0.100
Sodium Fluoride	0.020
Sorbitol Solution, U.S.P.	11.980
Glycerin	10.000
Sodium Saccharin, U.S.P	0.100
Pluronic FI27, NF	4.000
190 Proof Grain Alcohol, U.S.P.	7.000
Peppermint IFL2745	0.152
Caramel Color AP100	0.0085
Purified water	66.639

40

45

50

55 [0040] A typical semisolid formulation which is a cream: will include:

5	triclosan	0.1-5.3wt%
	Cetaryl glucoside and cetaryl alcohol (Emulgade PL 68/50, Henkel)	0.5-6.7wt%
	Cetaryl alcohol (Lanette, Henkel)	0.5-7.7wt%
	Coco-Caprylate (Cedol LC, Henkel)	0.5-6.0wt%
10	Dicapryl ether (Cetiet, Henkel)	0.25-5.0wt%
	Sweet almond oil	0.25-5.0wt%
	Petrolatum	0.5-6.0wt%
	Dimethicone (Silicone DC 200CS/Dow)	0.1-5wt%
15	Phase B	
	glycerin	0.5-4.6wt%
	Sodium methylparaben/Sodium paraben	0.01-0.03wt%
20	or	
	Sodium benzoate	0.25-0.3wt%
	Deionized water	10-90wt%

25 **[0041]** An example of a semi-solid formulation according to the invention is as follows:

30	Phase A	
	triclosan	0.3wt%
	Cetaryl glucoside and cetaryl alcohol (Emulgade PL 68/50, Henkel)	3.7wt%
	Cetaryl alcohol (Lanette, Henkel)	3.7wt%
35	Coco-Caprylate (Cedol LC, Henkel)	3.0wt%
	Dicapryl ether (Cetiet, Henkel)	2.0wt%
	Sweet almond oil	2.0wt%
40	Petrolatum	3.0wt%
	Dimethicone (Silicone DC 200CS/Dow)	0.6wt%

45	Phase B	
50	Glycerin	2.6wt%
	Sodium methylparaben	0.18wt%
	Sodium paraben	0.02wt%
55	Deionized water to	100.0wt%

Phase C
Tocopheryl acetate (cophenol 1260/Henkel) 1.0wt%

[0042] The composition is prepared by separately heating Phase A and Phase B to 80°C prior to forming these phases. Phase C is added with stirring at 55°C until a smooth homogeneous mixture is obtained.

[0043] The foregoing description of a preferred embodiment of the invention has been presented for purposes of illustration and description. It is not intended to be exhaustive or to limit the invention to the precise form disclosed. Obvious modifications or variations are possible in light of the above teachings. All such obvious modifications and variations are intended to be within the scope of the appended claims.

Claims

1. Use of triclosan or a combination of triclosan and an antimicrobial compound for the production of a composition for the treatment of mucositis, herpetic infections or fungal infections, especially candidiasis.
2. Use of triclosan according to claim 1 for the production of a composition for the treatment of mucositis in an immunocompromised patient.
3. Use according to claims 1 or 2 wherein triclosan is combined in a liquid formulation with a solubilizer.
4. Use according to claims 1 or 2 wherein the triclosan is in a semi-solid formulation.
5. Use according to anyone of the proceeding claims 1 to 4 wherein the composition includes a fluoride.
6. Use of triclosan for the production of a composition for treatment of mucositis in an immunocompromised patient according to anyone of the proceeding claims 1 to 5, said composition comprising a composition which comprises triclosan in an amount which is effective to alleviate the symptoms of mucositis and an amount of a fluoride compound which is effective to inhibit tooth decay in an immunocompromised patient.
7. Use according to anyone of the proceeding claims 1 to 6, wherein said composition comprise triclosan and a cationic antibacterial agent in amounts which are effective to alleviate the symptoms of mucositis, herpetic infections or fungal infections.
8. Use according to claim 7 wherein the cationic agent is selected from the group consisting of chlorhexidine, cetylpyridium chloride, benzalkonium chloride, benzethonium chloride, methylbenzethonium chloride and domiphen bromide.
9. Use according to claims 7 or 8 wherein the cationic agent is cetylpyridium chloride.
10. Use according to claim 9 wherein the triclosan and cationic agent are combined in a liquid formulation with a solubilizer.
11. Use according to claim 9 wherein the triclosan and the cationic agent are combined in a semi-solid formulation.



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 99 10 0030

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	EP 0 528 468 A (UNILEVER NV ; UNILEVER PLC (GB)) 24 February 1993 (1993-02-24)	1-10	A61K31/085
Y	* page 2, column 24-25; claims 1,3,4 *	1-11	A61K31/14
X	WO 93 25209 A (MESAROS JOZSEF & HM ; ERDELYINE MESZAROS KRISZTINA & (HU); FABULON) 23 December 1993 (1993-12-23)	1,3,4,7	A61K31/44
Y	* claim 1 *	1-11	/(A61K31/14, 31:085), (A61K31/44, 31:085)
	* page 7, line 16 - page 8, line 5 *		
	* page 1, line 5-10 *		
X	GB 2 160 099 A (TAKAOKA YOGO) 18 December 1985 (1985-12-18)	1,3,4,7	
Y	* claim 1 *	1-11	
	* page 2-3; example 1; table 2 *		
Y	US 5 279 813 A (GAFFAR ABDUL ET AL) 18 January 1994 (1994-01-18)	1-11	
	* abstract *		
Y	EP 0 577 306 A (LIBIN BARRY M) 5 January 1994 (1994-01-05)	1-11	
	* abstract *		
The present search report has been drawn up for all claims			TECHNICAL FIELDS SEARCHED (Int.Cl.6)
			A61K
Place of search	Date of completion of the search	Examiner	
MUNICH	12 August 1999	Herrera, S	
CATEGORY OF CITED DOCUMENTS			
<p>X : particularly relevant if taken alone</p> <p>Y : particularly relevant if combined with another document of the same category</p> <p>A : technological background</p> <p>O : non-written disclosure</p> <p>P : intermediate document</p> <p>T : theory or principle underlying the invention</p> <p>E : earlier patent document, but published on, or after the filing date</p> <p>D : document cited in the application</p> <p>L : document cited for other reasons</p> <p>& : member of the same patent family, corresponding document</p>			

EPO FORM 1503 03.82 (P4/C01)

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 99 10 0030

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

12-08-1999

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0528468 A	24-02-1993	AT 135569 T	15-04-1996
		AU 2081592 A	11-02-1993
		CA 2075551 A,C	09-02-1993
		DE 69209190 D	25-04-1996
		DE 69209190 T	08-08-1996
		JP 5194203 A	03-08-1993
		US 5240696 A	31-08-1993
WO 9325209 A	23-12-1993	HU 209370 B	30-05-1994
		AU 4352593 A	04-01-1994
GB 2160099 A	18-12-1985	JP 1495694 C	16-05-1989
		JP 61001615 A	07-01-1986
		JP 63044724 B	06-09-1988
		CH 664084 A	15-02-1988
		DE 3520325 A	12-12-1985
		FR 2565486 A	13-12-1985
US 5279813 A	18-01-1994	US 5135738 A	04-08-1992
		US 5167951 A	01-12-1992
		US 5496540 A	05-03-1996
		AT 398034 B	25-08-1994
		AT 296789 A	15-01-1994
		AU 632776 B	14-01-1993
		AU 4676889 A	05-07-1990
		CA 2006713 A	29-06-1990
		CH 679741 A	15-04-1992
		CN 1044223 A	01-08-1990
		DE 3942642 A	30-08-1990
		DK 671089 A	30-06-1990
		FI 98121 B	15-01-1997
		FR 2641187 A	06-07-1990
		GB 2227661 A,B	08-08-1990
		HK 172095 A	17-11-1995
		IE 63176 B	22-03-1995
		IT 1238355 B	13-07-1993
		JP 2288820 A	28-11-1990
		LU 87652 A	15-05-1990
		NL 8903186 A	16-07-1990
		NO 178953 B	01-04-1996
		PL 165411 B	30-12-1994
		PT 92736 A,B	29-06-1990
		SE 8904179 A	30-06-1992
		US 5260062 A	09-11-1993
		US 5234688 A	10-08-1993
		US 5273741 A	28-12-1993

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 99 10 0030

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

12-08-1999

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0577306 A	05-01-1994	US 5236699 A	17-08-1993
		CA 2098789 A	23-12-1993
		DE 69310443 D	12-06-1997
		DE 69310443 T	06-11-1997
		DK 577306 T	15-12-1997
		ES 2104063 T	01-10-1997
		MX 9303669 A	31-05-1994
		US 5855872 A	05-01-1999
<hr/>			